Dual blockade of the renin–angiotensin–aldosterone system in renal disease: what is the future?

To the Editor In their recently published paper, Lizakowski et al.,[1] a renowned research group that focuses on the renin–angiotensin–aldosterone system (RAAS) in renal disease, demonstrated that the dual blockade of the RAAS with different combinations of drugs had a similar effect on several clinical and laboratory parameters in patients with nondiabetic proteinuric chronic kidney disease (CKD) to that observed for angiotensin II receptor blocker monotherapy. A combination of telmisartan with aliskiren led to a marked elevation of plasma renin levels (as compared with telmisartan with perindopril, telmisartan with eplerenone, or telmisartan in monotherapy), but the increase did not translate into worsening of renal function, aggravation of proteinuria, or urinary loss of transforming growth factor β (TGF-β), the key mediator and biomarker of renal fibrosis. We agree with the authors that these data may suggest lack of direct nephrotoxicity of renin. The authors pointed to the safety of telmisartan with aliskiren in patients with nondiabetic proteinuric renal disease and made it the key message of the paper, although they were cautious to limit their conclusions to early stages of CKD and patients with low cardiovascular morbidity.

This study[1] adds new data to our current knowledge on therapeutic interventions on the RAAS. An extremely attractive, from the conceptual point of view, dual (or even triple) blockade of the RAAS in renal disease did not, however, translate into patient benefit in large-scale prospective clinical trials. The authors cited some of those "unsuccessful" studies in their paper (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [ALTITUDE] and Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [ONTARGET]).[2,3]

The renal community has often argued that, indeed, trials concerning dual RAAS blockade performed to date did not show benefits of this therapeutic approach, but in fact they were not designed to show renal benefit in carefully selected patients with well-defined renal disease. Hence, nephrologists were waiting for the results of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study.[4] In brief, the trial was performed exclusively in proteinuric patients with diabetic nephropathy (glomerular filtration rate [GFR] ranging from 30 to 89.9 ml/min/1.73 m^2, with patients equally distributed within the CKD stages: 2, 3a, and 3b). Patients were randomized to treatment with losartan (50–100 mg) plus placebo vs. losartan combined with escalated doses of lisinopril (10–20–40 mg). It should be emphasized that the trial incorporated detailed guidelines for investigators on how to proceed with subjects with any risk of hyperkalemia (the main "acute" threat of using dual RAAS blockade). Despite a precisely defined study group, careful methodology, and appropriate safety measures, the VA NEPHRON-D trial also failed to demonstrate any significant benefit from dual blockade of the RAAS in terms of nephroprotection and cardiovascular endpoints. As in many previous studies in the field, patients treated with dual RAAS blockade more frequently developed acute kidney injury and significant hyperkalemia.[4]

We think that a word of caution is needed before concluding on the safety of dual RAAS blockade because short-term safety of a carefully supervised small-size study group may not be reflected by large-scale, long-term clinical trials, or—particularly—everyday clinical practice.

The overall sound of the paper of Lizakowski et al.[1] is still in favor of dual RAAS blockade (although they acknowledged limitations of this approach). However, we wonder whether the studies by Lizakowski et al.[1] and Fried et al.[4] herald the end of the "dual-blockade" era and we can now put the nail in the coffin or whether there is still place for additional concepts, projects, and trials in this interesting research field. The question of whether the results obtained in proteinuric diabetic patients with quite advanced CKD (the VA NEPHRON-D study population) would be the same in proteinuric nondiabetic patients with early CKD (as in the study by Lizakowski et al.)[1] still remains open.

For many years, it has been argued that pleiotropic effects of the RAAS blockade are at least

as important as blood pressure lowering in protecting the kidneys. Recent studies have brought somewhat opposite conclusions: blood pressure control (independent of the drug class) seems to be critical for renal outcome, and—even more importantly—for the overall outcome of patients with renal disease (although RAAS-blocking agents still remain the first-choice antihypertensive drugs in this population).[5,6]

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Conflict of interest The authors declare no conflict of interest.

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